Environmental Tobacco Smoke and Low Birth Weight: A Hazard in the Workplace?

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Low birth weight (LBW) increases infant morbidity and mortality worldwide. One well-established risk factor is maternal smoking. Environmental tobacco smoke (ETS) exposure has recently been focused on as another potential risk factor. In this article, we review epidemiologic literature on the effects of ETS on LBW and intrauterine growth retardation (IUGR), the cause of LBW related to maternal smoking. As we consider the feasibility of modifying women's exposure, we focus our discussion on workplace exposure to ETS. The workplace is particularly important to consider because women of child-bearing age are present in the workplace in greater numbers now than ever before. In addition, certain subgroups of working women may be particularly at risk from the effects of ETS on pregnancy because they work in environments with higher exposure or they are more susceptible to its effects. We conclude that there is consistent evidence to relate maternal ETS exposure to an increased risk of adverse pregnancy outcomes and that this association may be generalized to the work environment. In studies with positive findings, infants exposed to ETS antenatally were 1.5–4 times more likely to be born with LBW, but few studies examined LBW. Most studies looked at measures of IUGR. ETS was associated with reductions in birth weight (adjusted for gestational age) ranging from 25 to 90 g. Infants born to women exposed to ETS were generally 2–4 times more likely to be born small-for-gestational age. ETS exposure in the workplace can and should be minimized to protect pregnant women from its adverse effects. *Key words*: birth weight, cotinine, environmental tobacco smoke, intrauterine growth retardation, low birth weight, nicotine, passive smoke, pregnancy, small for gestational age, smoking, women, workplace. — *Environ Health Perspect* 107(suppl 6):879–904 (1999). http://ehpnet1.niehs.nih.gov/docs/1999/suppl-6/897-904misra/abstract.html

Low birth weight ([LBW] < 2500 g) is the leading cause of infant mortality in the United States. Approximately 7.4% of all births in 1995 were LBW, a proportion that has changed little in the past two decades (*1*). Smoking is one of the few modifiable risk factors for LBW. There is an abundance of evidence linking maternal smoking to LBW with relative risk estimates in the range of 2–4 (*2*). Two unfavorable birth outcomes, not mutually exclusive, result in low birth weight: preterm delivery and intrauterine growth retardation (IUGR). The adverse effects of maternal smoking on LBW appear to operate through an effect on IUGR rather than through an effect on preterm delivery. Maternal smoking has consistently been demonstrated to increase the risk of IUGR and to reduce mean birth weight by approximately 150–250 g (*2*). There is a dose–response relationship between maternal smoking and adverse pregnancy outcomes with a stepwise increase in risk with an increased number of cigarettes smoked per day (*2*). However, the timing of the exposure (maternal smoking) influences its effects on pregnancy outcomes. The adverse effects on LBW and IUGR are largely limited to smoking in the second half of pregnancy; women who quit smoking by the second half of pregnancy do not have an increased risk of poor outcomes (*3–5*). The biologic mechanism by which maternal smoking causes growth retardation has not been definitely established. The current evidence suggests that the impairment of growth associated with maternal smoking results from reduced oxygen flow to the fetus. The maternal blood supply to the placenta is reduced and its oxygen load attenuated by the increased maternal carboxyhemoglobin levels associated with maternal smoking (*2,6*). This association between maternal smoking and LBW fulfills many of the causal criteria (strength of association, consistency, dose response, reversibility, and biologic plausibility) and has been judged to be causal in the Surgeon General's report (*3*).

The weight of evidence linking maternal smoking with LBW has led to concern about the effects of environmental tobacco smoke (ETS). In addition, many of the chemicals in cigarette smoke, including nicotine and carbon monoxide, are present in higher concentrations in undiluted sidestream smoke than in the (mainstream) smoke inhaled by the smoker (*7,8*). Of course, ETS comprises diluted sidestream smoke and exhaled mainstream smoke. Early studies (1960s) reported small effects on birth weight associated with *in utero* exposure to paternal smoking among nonsmoking mothers (*9,10*). These studies were limited in their ability to assess exposure and to control for potential confounders. Beginning in the 1980s, as effects of ETS on

children were recognized, there has been renewed interest in this issue. Studies of ETS and pregnancy outcomes have generally continued to be based on a woman's report of ETS exposures, although sources of ETS other than the father's smoking have been considered. Recently, a few studies have incorporated biomarkers of exposure, either cotinine (a nicotine metabolite) or nicotine levels in the pregnant or postpartum woman. ETS exposure in pregnant women increases levels of nicotine and cotinine in pregnant women and in their amniotic fluid (*11,12*). In most studies of ETS and pregnancy, birth weight adjusted for gestational age (a proxy for IUGR) or birth weight alone has been the focus with LBW itself less frequently examined. Based on the studies of maternal smoking, IUGR (assessed by small-for-gestational age [SGA] [e.g., < 5th or < 10th percentile of birth weight for gestation, > 2 SD (standard deviation) below the mean birth weight for gestation] or birth weight adjusted for gestational age) and LBW are indeed the most appropriate outcomes to consider.

Review of ETS–LBW Literature

A review of the published literature on the relationship between ETS and LBW, birth weight, and IUGR (Table 1) was completed using the MEDLINE database (National Library of Medicine, Bethesda, MD) through 1998 and the bibliographies of individual papers. We a priori defined criteria for inclusion of a study to synthesize the current state of knowledge. These criteria were applied to all studies regardless of their findings. Studies were excluded if they did not *a*) describe clearly how the exposure to ETS was determined (no such studies in fact were found); *b*) clearly separate active smokers exposed to

Table 1. Review of the literature.

First author	Design	n	Exposure	Outcome	Confounders	Effect size
Ahlborg (47)	Prospective cohort	4,107	Self-report ETS 17.3% total sample 31% nonsmokers	LBW	Maternal age, education, parity, spontaneous abortion history, planned pregnancy, residence, working status, alcohol, coffee	Relative risk, 95% CI Smoking partner: 0.84 (0.3–2.2) ETS at work, no ETS at home 1.21 (0.3–5.2) ETS at work in late pregnancy 1.8 (0.5–6.3)
Ahluwalia (39)	Cross-sectional	17,412	Self-report ETS 31% overall	LBW	Maternal race, education, parity, marital status, weight gain, prepregnancy BMI, alcohol; stratified by maternal age	Odds ratio, 95% CI Mothers 30 years old: any ETS 2.4 (1.5–3.9) Mothers <30 years old: any ETS 0.9 (0.8–1.1)
Brooke (36)	Prospective cohort	1,513	Self-report ETS 28% nonsmokers	Birth weight ratio (observed/ expected)	Maternal height, parity, infant sex	Birth weight ratio ETS: 1.050 Birth weight ratio no ETS: 1.055 F statistic comparison, p = 0.56
Campbell (31)	Cross-sectional	518	Self-report ETS 46.5% total sample 36.7% nonsmokers	Birth weight	Maternal age, social class, parity, alcohol, infant sex	Mean difference in BW, 95% CI Paternal smoking: –113 g (–216, +8)
Chen (62)	Case-control	111 cases 124 controls	Self-report ETS Work 14.5% Home 15.3% In car 11.1% "Other" 35.2%	SGA: <10th percentile in term infants (IUGR)	Maternal age, income, employment, parity, weight gain, prepregnancy weight, alcohol, prenatal care	Odds ratio, 95% CI 0.1–1.9 hr/wk: 0.55 (0.23–1.32) 2–5.9 hr/wk: 0.48 (0.20–1.15) 6–29.9 hr/wk: 0.58 (0.24–1.39) 30 hr/wk: 0.50 (0.14–1.74)
Dejin-Karlsson (37)	Prospective cohort	826	Self-report ETS 65.9% total sample (at work or at home)	SGA: >2 SD below mean (IUGR)	Maternal age, nationality, weight, height, education	Odds ratio, 95% CI 3.9 (1.4–10.7)
Eskenazi (27)	Prospective cohort	3,529	Serum cotinine 2–10 ng/mL 3.3% total sample 5.1% nonsmokers	Birth weight adjusted for gestational age (IUGR)	Maternal age, race, education, employment, parity, BMI, alcohol, coffee, partner smoking, infant sex	Mean difference in BW, 95% CI –45 g (–125.6, +36.0)
Fortier (52)	Cross-sectional	4,644	Self-report hours per week among nonsmokers 1–14 hr/wk work: 18.7% 15–34 hr/wk work: 7.4% 35+ hr/wk work: 8.8%	SGA: <10th percentile sex specific (IUGR)	Maternal age, education, parity, SGA history, alcohol, caffeine, paid work, weeks working, work schedule, lifting, standing	Odds ratio, 95% CI Any ETS: 1.09 (0.9, 1.3) 1–14 hr/wk: 1.13 (0.7, 1.6) 15–34 hr/wk: 1.17 (0.7, 1.9) 35+ hr/wk: 1.36 (0.9, 2.1)
Haddow (32)	Prospective cohort	1,231	Serum cotinine 1–9.9 ng/mL 31.4% total sample	Birth weight	Maternal age, education, gravidity, weight, infant sex	Mean difference in BW, 95% CI –104 g (–173, –35)
Lazzaroni (26)	Prospective cohort	1,004	Self-report hours/day 25% total sample exposed any	Birth weight adjusted for gestational age (IUGR)	Maternal age, parity, weight, height, weight gain, alcohol, complications, infant sex, paternal weight, height, employment, education	Mean difference in BW, 95% CI –16.9 g/hr ETS (–35, 1.3) >1 hr ETS/day: –61.3 g (–26.8, 149.3)
Mainous (19)	Retrospective cohort	3,253	Self-report perceived frequency 23% never 46% occasionally 17% often 13% always	LBW	Maternal age, family income	Odds ratio, 95% CI Always exposed: 1.57 (0.98–2.51) Nonwhites, always exposed: 2.3 (1.06–4.99)

(Continued)

Table 1. Continued.

First author	Design	n	Exposure	Outcome	Confounders	Effect size
Martin (30)	Prospective cohort	3,891	Self-report ETS 2 hr/day 23.6% nonsmokers	LBW Birth weight	Maternal age, marital status, ethnicity, education, employment, alcohol	Odds ratio, 95% CI Term births, ETS 2 hr/day: 2.2 (1.1–4.5) Mean difference in BW, 95% CI term births, ETS 2 hr/day: −24 (−59.9, 12.8)
Martinez (28)	Prospective cohort	1,219	Self-report paternal smoking 21% nonsmokers	Birth weight adjusted for gestational age (IUGR)	Maternal age, parental education, birth rank, ethnicity, infant sex	Mean difference in BW, 95% CI Paternal smoking Any: −34 g (−63, −5) 1–10 cigarettes/day: −29 g 11–20 cigarettes/day: −82 g 20+ cigarettes/day: −88 g Test for trend, $p = 0.03$
Matthai (25)	Prospective cohort	994	Self-report paternal smoking 52% nonsmokers	Birth weight adjusted for gestational age (IUGR)	Maternal age, height, infant sex	Mean difference in BW, 95% CI −63 g (−12, −114)
Nafstad (38)	Case-control	58 cases 105 controls	Nicotine (hair) 0.75–4 µg/g 58% nonsmokers >4 µg/g 8.2% nonsmokers	SGA: < 10th percentile (IUGR)	Marital status (others considered but excluded)	Odds ratio, 95% CI 0.75–4 µg/g (2nd & 3rd quartile): 3.4 (1.3, 8.6) >4 µg/g (4th quartile): 2.1 (0.4, 10.1)
Ogawa (35)	Cross-sectional	5,336	Self-report ETS 2 hr/day (home, work, or elsewhere) 35% nonsmokers	Birth weight LBW	Maternal age, height, parity, occupation, alcohol use, gestational age (term births only) Maternal age, height, parity, occupation, alcohol use, gestational age (term births only)	Mean difference in BW, 95% CI Term births: −10.8 g (no CI) (not significant) Odds ratio, 95% CI Term births: 1.0 (0.7–1.5)
Rebagliato (24)	Prospective cohort	690	Salivary cotinine 1.8–14 ng/mL 19.3% nonsmokers	Birth weight adjusted for gestational age	Maternal age, height, prepregnancy weight, education, social class, illness in pregnancy, infant sex	Mean difference in BW, 95% CI 1.8–14 ng/mL: −87.3 (−173.5, −1.1)
Rubin (33)	Cross-sectional	500	Self-report ETS 46% total sample	Birth weight	Maternal age, social class, parity, alcohol, tobacco, antenatal illness, infant sex	Mean difference in BW, 95% CI Paternal smoking: −6 g cigarette/day (−0.12, −11.88) −120 g pack/day (−237.4, −2.4)
Windham (23)	Retrospective cohort	992	Self-report ETS 30% nonsmokers	Birth weight adjusted for gestational age LBW LBW at term	Race, alcohol, caffeine Race, alcohol, caffeine	Mean difference in BW, 95% CI +13.8 (−53.8, +81.4) 1.0 (0.52–2.11) 1.8 (0.64–4.80)
Zhang (29)	Case-control	1,785	Self-report paternal smoking 58% nonsmokers	Birth weight adjusted for gestational age (IUGR)	Maternal age, parity, occupation	Mean difference in BW, 95% CI −30 g (−7, 66)

BW, birth weight.

ETS from nonsmokers exposed to ETS (*13*); *c*) consider potential confounders such as socioeconomic status (*14–18*), birth weight analysis only (*19*); *d*) provide no assessment of statistical significance (*10,15,17,20,21*); or *e*) characterize the study population (*21,22*).

Recent studies of ETS generally show an adverse effect of exposure on LBW, birth weight, and IUGR, although as would be expected, the effect sizes are smaller than for maternal smoking. Even in those studies in which the effects were not statistically significant, ETS was consistently associated with small effects in the direction of increased risks for adverse outcomes (reductions in birth weight, increases in risk of LBW or IUGR).

Studies of ETS exposure and birth weight fall into two groups: birth weight adjusted for gestational age (*23–30*) or birth weight unadjusted for gestational age (*31–33*). Obviously the difference in birth weight will be larger if birth weight is not adjusted for gestational age. More important, when birth weight is adjusted for gestational age, this parameter becomes an estimate of fetal growth as it relates size (weight) with time (gestational age). Without adjusting for gestational age, we cannot determine whether birth weight is reduced among women exposed to ETS as a result of growth restriction or if it is the result of early delivery. Given that the effects of maternal smoking appear to relate only to growth restriction and not to preterm delivery (*2,34*), we expect a similar effect of ETS exposure, although it is possible that the mechanisms of effect might differ. Furthermore, because study samples often differ in their gestational age distributions, a failure to adjust for gestational age could result in different estimates of the effects of ETS across studies. For this reason alone, the literature may appear inconsistent.

In 4 of the 11 studies examining the effect on birth weight (adjusted and unadjusted for gestational age), the reductions in birth weight were statistically significant (Figure 1, Table 1). Although not all of the differences in mean birth weight were statistically significant, the estimates of the difference in mean birth weights for 10 of the 11 studies were negative, falling between –25 and –125 g. In the three studies (*31–33*) that examined ETS effects on birth weight unadjusted for gestational age, the effects of ETS were very similar, with point estimates clustering around –105 g. When adjusting for gestational age, the size of the effect was smaller and more variable, ranging between –25 and –87 g. A recently published meta-analysis (*23*) calculated average birth weight decrements associated with ETS exposure in nonsmoking mothers. Based on studies that adjusted for confounders, the pooled birth weight difference was –28.5 g (95% confidence interval

[CI]: –40.8, –16.2). Limiting the meta-analysis to those studies that considered multiple sources of ETS exposure and adjusted for confounders, the pooled birth weight difference was –24 g (95% CI: –39.3, –8.6) (*23*). Both of these estimates of the birth weight difference are statistically significant. Although this difference in birth weight is not large and may not be clinically significant for any individual infant, the birth weight distribution is shifted down with exposure to ETS. Such a shift on a population level would lead to increases in LBW, a significant effect of ETS for the population. It is unclear whether the meta-analysis was limited to studies that adjusted for gestational age.

IUGR can be examined using either a continuous measure, such as birth weight adjusted for gestational age, or a dichotomous measure, such as SGA (< 5th or < 10th percentile of birth weight for gestational age, > 2 SD below mean birth weight for gestational age). Many of the studies described in the preceding paragraph and in Figure 1 are in essence studies of IUGR, as birth weight is adjusted for gestational age. In three (*24,25,28*) of the eight studies that examined ETS effects on birth weight adjusted for gestational age, the effect was statistically significant (Figure 1, Table 1). In two (*30,35*) of the five studies with nonsignificant effects of ETS on birth weight, the sample of births was restricted to term (> 37 week) deliveries. The effect on birth weight of any exposure is usually smaller when restricted to this pool of deliveries, as there is less variability in birth weight after 37 weeks gestation. The point estimates of the difference in mean birth weights for all eight of the studies were negative, with the point estimates ranging between –25 and –90 g.

Another less frequently used continuous estimator of IUGR is the birth weight ratio.

The numerator is the birth weight observed at a given gestational age, and the denominator is the birth weight expected at a given gestational age (the mean birth weight). Brooke and colleagues (*36*) examined the effect of ETS on this birth weight ratio measure and found no significant difference in the birth weight ratio related to ETS. This study is difficult to place in context because its methods are quite different from those of other studies in this area; in particular, the birth weight ratio is not a widely accepted estimator of growth retardation.

Four studies examined the effect of ETS on IUGR, using dichotomous measures of SGA (Figure 2, Table 1). Two (*37,38*) of the four studies reported strong (relative risk estimates 3–4) and statistically significant associations, notably one of which used a biomarker for exposure (*38*). The effects of ETS on LBW (a dichotomous variable) have also been less often studied than the effects on birth weight measured as a continuous variable (Figure 3, Table 1). In three (*19,30,39*) of the six studies, the odds of LBW were significantly and substantially increased for infants born to women exposed to ETS, although in two of the studies the significant effect was only in a subgroup of the women [women over 30 years of age (*39*), nonwhite women (*19*)]. Three of the studies examined LBW only in term infants or in term infants separately (*23,30,35*); this is a subset of LBW that overlaps with IUGR. (Infants born LBW at term are by definition SGA and growth retarded.) The risk of a LBW infant at term was increased in two studies (*23,30*), albeit significant at =0.05 for only the Martin and Bracken study (*30*). Overall, considering findings for both LBW and LBW at term, relative risk estimates for five of the six studies showed an increase in risk. The meta-analysis by Windham et al. (*23*) adds further evidence
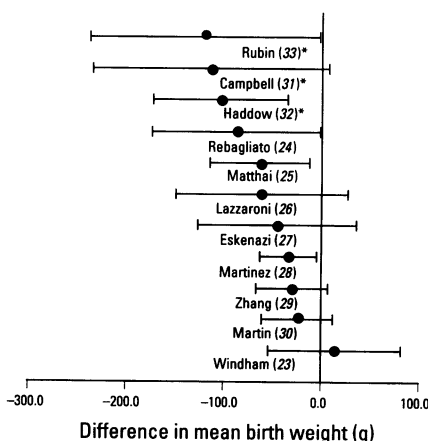
Figure 1. Difference in mean birth weight related to environmental tobacco smoke exposure. Studies labeled by first author as given in Table 1. Studies with an asterisk (*) are not adjusted for gestational age.
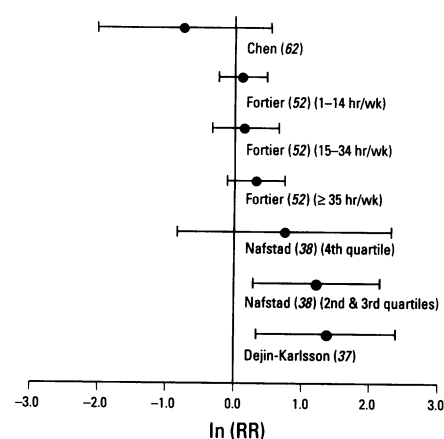
Figure 2. The natural logarithm of the relative risk estimates for small-for-gestational age related to environmental tobacco smoke exposure. Studies labeled by first author as given in Table 1.

of an effect on LBW. The pooled odds ratio (OR) for the studies of LBW that adjusted for confounders was 1.38 (95% CI: 1.01–1.87).

Exposure Measure

Differences in the method of determining exposure to ETS may account for some of the inconsistencies among these studies; they may also indicate which studies' results are more relevant to reaching a conclusion about the effects of ETS. Many of the studies relied on self-report to assess exposure to ETS. Use of self-report measures rather than biomarkers may lead to differential or nondifferential misclassification. Nondifferential misclassification would attenuate real associations between ETS and birth outcomes. If exposure is differentially underestimated using self-reported measures, attenuation of the association between ETS and birth outcomes could also occur. It is also more difficult to compare self-reported exposure across studies, as the questions and categories were rarely similar.

More recently, studies have used either biomarkers alone or both biomarkers and self-report. To date, primarily two biomarkers of exposure have been assessed in pregnant women: cotinine, a nicotine metabolite; and nicotine, a component of cigarette smoke. Numerous studies have established cotinine and nicotine as valid biomarkers for maternal cigarette smoking (40–42). It should be noted, however, that bodily fluid (e.g., blood, urine, saliva) cotinine levels reflect exposure over a 2- to 3-day period (half-life ~ 17 hr) and therefore may not capture chronic exposure adequately (41). Blood levels of nicotine are the most accurate proxy for the dose of nicotine absorbed from ETS exposure. However, most studies of ETS have used saliva or urine concentrations because these samples have been found to be valid substi-

tutes and are easier to obtain (41). Nicotine in bodily fluids alone has a very short half-life (~ 2–3 hr) and therefore can measure only the most acute exposures (41). However, nicotine levels assessed in hair do not have this same limitation and nicotine levels in hair reflect tobacco smoke exposure over the past few months (43–46). A biomarker assessment of ETS may also be more valid than self-reported exposure because it can account for differences in exposure not captured by reporting the number of hours one is exposed to ETS. For example, differences in ventilation of the environment can affect the biologic burden received and would be ignored by a self-reported assessment of exposure. Compared to self-report, differential misclassification would be much less likely and nondifferential misclassification also relatively less likely. However, biomarkers integrate all sources of exposure and cannot separate different sources. Self-reported assessment is crucial if one wishes to study effects of exposure by specific source (e.g., home, workplace).

Among the four studies that used biologic measurements rather than self-report, three reported significant associations with adverse pregnancy outcomes. Nafstad et al. (38) found a significant increased risk of SGA (growth retardation) associated with high nicotine levels in hair, categorized in quartiles, in nonsmokers. Rebagliato et al. (24) found a significant reduction in birth weight, adjusted for gestational age, associated with high cotinine levels, also categorized in quintiles, in nonsmokers. This is consistent with the findings of Haddow et al. (32) who reported that high serum cotinine levels in nonsmokers were associated with significantly decreased birth weight adjusted for gestational age. Eskenazi et al. (27) also used serum cotinine, classified dichotomously (2–10 ng/mL vs < 2 ng/mL) to assess ETS exposure but found no significant effect on the outcome. The dichotomous categorization in the Eskenazi et al. study (27) may have also diluted a real effect of higher level exposures by including possibly hazardous lower level exposures with the reference group (< 2 ng/mL). The reference groups for the cotinine studies reporting significant adverse effects [Rebagliato et al. (24) and Haddow et al. (32)] were restricted to the lowest levels of cotinine (0–0.5 ng/mL). Statistical power may have been limited in the study by Eskenazi et al. (27), as only 5.1% of nonsmokers were classified as exposed to ETS based on cotinine levels (2–10 ng/mL). This is in contrast to the Rebagliato et al. study (24) in which the prevalence of exposure in the highest quintile was nearly 20% (1.8–14 ng/mL) and the Haddow et al. study (32) in which prevalence of exposure to ETS based

on cotinine was 31.4% (1–9.99 ng/mL). The upper levels for the studies of Rebagliato et al. and Eskenazi et al. also differ, with Eskenazi et al. (27) excluding women with levels over 10 ng/mL and Rebagliato et al. (24) excluding those over 14 ng/mL as possibly active smokers. The exclusion of women in the 10–14 ng/mL range may also have contributed to the smaller effect size seen in the Eskenazi et al. study (27) compared to the Rebagliato et al. study (24).

Critical Period of Exposure

The timing of the ETS exposure is an important issue addressed explicitly by only one of the studies. Studies of maternal smoking in pregnancy have consistently shown that it is only smoking in the second half of pregnancy that exerts a significantly adverse effect on LBW, IUGR, and birth weight (4,5). Therefore, one might also expect ETS exposures limited to the first half of pregnancy to exert little or no effect. Failure to separate early and late exposures might dilute the estimated effects. There is reason to expect that ETS exposures might change over the course of pregnancy, particularly ETS exposure in the workplace. Women may stop working as their pregnancy progresses and partners and co-workers might reduce their smoking around a woman as she becomes visibly pregnant. Nonsmoking pregnant women might become more active in their attempts to reduce ETS exposures as their pregnancy progresses. The one study (47) that explicitly examined ETS in late pregnancy found an increased risk of LBW, albeit not significant, of workplace ETS exposure in later pregnancy (OR = 1.83) but no substantial increase in risk for workplace ETS exposure overall (OR = 1.21). Although the other studies reviewed did not explicitly examine ETS exposures by gestation, the questions and timing of interviews and/or biomarker assessment offer some clues. Nearly all the interview studies asked women about their exposures generally during pregnancy and did not specify the time period of interest. In two studies, those by Ahluwalia et al. (39) and Martin and Bracken (30), the questions were asked at the first prenatal visit. Neither article provides information on the mean gestational age at first visit. However, even with low income populations in the United States, which comprised the study population, most women obtaining prenatal care do so before the 20th week of pregnancy. A study conducted in Sweden (37) also asked about ETS at the first prenatal visit and noted that the mean gestational age at first visit was 12 weeks. Therefore, these three studies presumably assessed ETS exposure in the first half of pregnancy. The Haddow et al. study (32) relied on serum cotinine measured in the
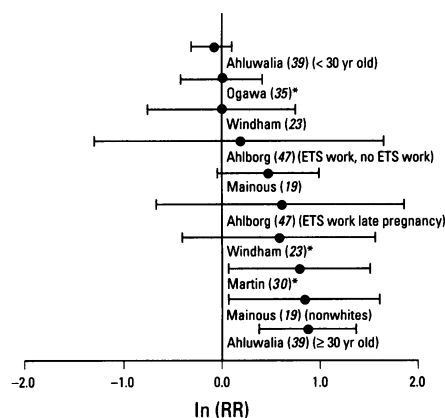
Figure 3. The natural logarithm of the relative risk estimates for low birth weight related to environmental tobacco smoke exposure. Studies labeled by first author as given in Table 1. Studies marked with an asterisk (*) represent LBW at term only.

second trimester and also presumably assessed exposure in the first half of pregnancy. All these studies found strong adverse effects of ETS that might suggest that exposure to ETS did not change during pregnancy. The Martinez et al. study (28), which interviewed families postnatally about paternal smoking and ETS assessment, would be expected to represent the entire pregnancy with a possible bias toward representing exposure in the latter part of pregnancy due to length of recall. In this study, a statistically significant trend of decreasing birth weight with increasing exposure dose was reported. Two of the studies employing biomarkers collected their samples in the third trimester: Eskenazi et al. (27) analyzed cotinine from samples collected at 27–28 weeks gestation and Rebagliato et al. (24) analyzed cotinine from samples collected in the third trimester. The Eskenazi et al. study (27) reported no significant association between high levels of cotinine and birth weight, whereas the Rebagliato et al. study (24) found a significant reduction in birth weight associated with similar levels of cotinine. Nafstad et al. (38) collected hair samples for nicotine analysis in the immediate postpartum period, which would represent the few months of exposure. Presumably, then, the measure of ETS in the Nafstad et al. study (38) would capture exposure in the last trimester of pregnancy. As noted above, this study did find a strong association between nicotine level and risk of SGA.

Outcome Measure

The choice of outcome measure is also important to consider. Overall, there appear to be stronger effects of ETS on LBW and SGA than on birth weight (adjusted or not for gestational age). This difference is informative and may help us to understand how ETS exposure acts. The discrepancies in findings suggest that the reduction in birth weight is not uniform across the full distribution of birth weight. A uniform reduction in birth weight across the distribution of birth weight would result in some increase in LBW or SGA. The size of the effect of ETS exposure on LBW and SGA is often large, however, with ORs of 2 or greater. This effect is more similar to effects seen for maternal smoking during pregnancy, whereas the birth weight effects are much smaller than those for maternal smoking. Perhaps the reduction in birth weight is larger for infants at the lower end of the birth weight distribution. Martin and Bracken (30) also observe that while the decrease in birth weight is relatively small compared to that of direct maternal smoking, the reduction "appears to operate on the low end of the birth weight distribution, thereby increasing risk" of LBW. Perhaps infants born in the lower end of the birth weight

distribution are more likely to be exposed to ETS, and several studies have previously demonstrated that women of low socioeconomic status are at increased risk for LBW (48). The stronger effect of ETS on LBW compared to birth weight is also important with regard to infant outcomes. Although reductions in birth weight are associated with increases in infant mortality across the entire birth weight continuum, reductions in birth weight that lead to LBW are much more hazardous. Approximately two-thirds of all infants deaths in the United States in 1995 occurred to infants born with LBW (1). Infants born with LBW are also more likely to have neurodevelopmental problems such as cerebral palsy (49). Therefore, the effects of ETS on LBW are relatively more important in terms of policy than the effects of ETS on birth weight alone.

Confounding

All these studies have considered the potential for confounding of the association between exposure to ETS and birth outcomes. In many of the studies, a wide range of covariates have been included in the final models to produce unconfounded estimates of effect. The obvious potential confounders have been considered. There is some risk, however, that these studies may have controlled for covariates that should not be considered confounders but rather are part of the causal pathway. This may be particularly true of studies considering ETS in the workplace. ETS exposure may indeed be higher in workplaces in which working conditions are more strenuous. Increased ETS levels may be the result of these working conditions and controlling for them in the analysis may remove the very real effects of ETS. This is especially problematic with regard to socioeconomic status. As stated earlier, socioeconomic status is a very strong predictor of LBW risk and also may be related to ETS exposure. The higher ETS exposure levels may be part of the explanation for the increased risk of LBW to women of low socioeconomic status. Therefore controlling for socioeconomic status would mask a real effect of ETS.

Statistical Power

Given that the effect size is likely small and the prevalence of exposure may vary depending on the population, inadequate statistical power to detect the effects may be a source of inconsistency in the findings reported for ETS and birth outcomes. The only one of the four studies using a biomarker that did not find a significant effect of ETS had an extremely low rate of exposure (less than 10% of women were classified as exposed based on the cotinine levels in the Eskenazi study).

Discussion

LBW increases infant morbidity and mortality worldwide. One well-established risk factor is maternal smoking. ETS exposure has recently been focused on as another potential risk factor. As we consider the feasibility of modifying women's exposure, we have focused our discussion on workplace exposure to ETS. The workplace is particularly important to consider because women of child-bearing age are present in the workplace in greater numbers than ever before. In 1994 (the most recent data available), there were 60 million women in the U.S. labor force and those women made up 46% of the total U.S. labor force. Between the ages of 20 and 44, the peak child-bearing years for women, labor force participation rates exceeded 70% for women (50). In addition, certain subgroups of working women may be particularly at risk from the effects of ETS on pregnancy because they work in environments with higher exposure or are more susceptible to its effects. In 1994, 10 million American women worked in the service industry, 4.3 million worked as machine operators, fabricators, or laborers, and 1.2 million worked in precision production, craft or repair trades (50), workplaces in which ETS may still be a problem.

This discussion evaluates the charges given to the participants in the July 1998 U.S. Occupational Safety and Health Administration workshop on ETS in the workplace and health outcomes. Three specific charges were given in the area of low birth weight: (1A) "What is the dose-response relationship for ETS exposure and LBW?"; (1B) "Are exposures in the workplace in a range of biologic concern?"; (2) "Are there studies of occupational exposure to ETS and LBW?"; (3) "Can results from studies of birth weight and ETS exposure generally be extended to the workplace?".

Charge 1A: What Is the Dose–Response Relationship for ETS Exposure and LBW?

A critical examination of studies done to date and with greater weight placed on studies with fewer methodologic limitations leads this reviewer to conclude that there is a consistent and plausible association between ETS and LBW. The recent meta-analysis and qualitative literature review by Windham et al. (23) also comes to the same conclusion, suggesting an average increase in LBW of approximately 38%. In response to the first part of this charge, determination of a dose–response effect, the evidence is somewhat weaker. Few of the studies published appear to have examined this issue. However, unless ETS exposure influences birth weight through a different mechanism than does maternal smoking, we would expect a

dose–response pattern similar to what is found for maternal smoking exposure. A caveat to this is that ETS exposures might be constrained to such a limited and low level as to make dose–response effects too subtle to detect and perhaps even of little relevance. Only five of the studies with positive findings (statistically significant associations of ETS exposure with birth outcomes) collected and analyzed the ETS exposure data in such a way as to examine the possibility of dose–response patterns. Both studies using interview data (28,33) and one study using biomarkers of exposure data (24) found some evidence of a dose–response trend.

Charge 1B: Are Exposures in the Workplace in a Range of Biologic Concern?

To respond to the latter part of the first charge, we need information on workplace ETS exposure levels for pregnant women. Although most studies report ETS exposure as the number of hours of exposure per day, we can only consider these data as surrogates for exposure levels (51). To determine if workplace exposures are in a range associated with risk, we would need studies that measure biomarker levels in pregnant women as proxies for levels of ETS in the workplace. The most appropriate biomarker of ETS exposure for pregnant women is not certain, as it is unclear which components of cigarette smoke are responsible for the reduction in fetal growth. Nicotine and carbon monoxide are the two components best established as relating to the adverse effect of maternal smoking. In terms of biomarkers, the best established for use in studies of ETS and pregnancy are nicotine and its metabolite, cotinine. Measures of carbon monoxide have not been used in studies of pregnant women. Benowitz (41), in a review of the validity of cotinine as an ETS biomarker, argues that carbon monoxide in the blood is a nonspecific and insensitive marker of ETS exposure. Therefore, although the effects of ETS may operate in part through carbon monoxide, carbon monoxide may be problematic as a best biomarker of ETS exposure in pregnancy.

To establish whether levels of ETS exposure in the workplace are hazardous, we need to first determine what level of cotinine or nicotine, the two relevant biomarkers, represents a hazardous level of exposure for a pregnant woman. Based on the studies using cotinine as a biomarker, it appears that adverse effects are most likely reached when cotinine levels exceed 1.7 ng/mL, although they may be reached at lower levels. Studies of self-reported ETS exposure that considered dose–response effects do not provide consistent guidance. Even if we can reach a conclusion about what level is hazardous, we must

then determine whether the workplace can produce levels of this magnitude. Studies would be needed of nonsmoking pregnant women exposed to ETS only in the workplace. In these studies, cotinine or nicotine levels could be measured across a variety of workplace environments. Furthermore, the fetus may be more or less susceptible to a given level of ETS absorbed by the mother (measured as cotinine or nicotine) due to differences in placental hemodynamics or other interactions with the maternal–uterine–placental environment. Given these challenges, the two most feasible approaches to protect pregnant women would be to either a) rely on standards developed for nonpregnant adults with regard to health outcomes for which more data are available; or b) assume all ETS exposure is unsafe for pregnant women, as the data from two of the best and most recent studies (24,32) indicate that even low levels of maternal cotinine (1–2 ng/mL) are hazardous.

Charge 2: Are There Studies of Occupational Exposure to ETS and LBW?

There are two primary sources of ETS exposure for pregnant women: exposure in the home and exposure in the workplace. Self-reported measures of ETS exposure can separate home from workplace exposures. Biologic measures of ETS exposure integrate all sources of ETS exposure (home, work, public spaces) as well as maternal smoking exposure (unless women who smoke are excluded). Therefore studies that relied on biomarkers alone cannot differentiate the effects of occupational exposure from other sources of ETS exposure. In the studies that included self-reported measures, only two separated occupational exposure to ETS from other ETS exposure (47,52). It is worth noting that in both these studies, exposure in the home alone did not appear to have adverse effects on pregnancy; but there were effects, albeit small effects, of exposure in the workplace alone. One of the two studies (52) also showed a dose–response trend, with an increasing risk of a SGA infant being born as the number of hours of workplace ETS exposure increased.

Charge 3: Can Results from Studies of Birth Weight and ETS Exposure Generally Be Extended to the Workplace?

There are no obvious reasons why such studies could not be generalized. The potential for interactions between ETS and other workplace exposures is the primary factor that would complicate extrapolations of nonoccupational studies. It may be that there are workplace exposures that act synergistically to

magnify the effect of ETS on birth weight. These exposures could be other airborne pollutants as well as any of a number of chemical exposures in the workplace. Stress, physical or psychologic, is another factor that could interact with ETS exposure to increase the adverse effects on birth weight. There is one important interaction that has been examined in past studies that may be particularly relevant to pregnant workers and that is the interaction between smoking and maternal age. One study of ETS (39) has shown an interaction between maternal age and ETS exposure such that ETS more than doubled the risk of LBW (OR = 2.4; 95% CI = 1.5, 3.9) for older women (30 years of age) while having no adverse effect on outcomes for younger women (OR = 0.9; 95% CI = 0.8, 1.1). These data are not inconsistent with studies of maternal smoking that show adverse effects for women of all ages but find stronger effects among older women (53). As U.S. women increasingly choose to delay their first birth (54), this interaction may be very important to consider when establishing policies.

Poverty might also act to enhance the risk of ETS exposure. Poor women are a vulnerable population with regard to adverse pregnancy outcomes. Women of lower socioeconomic status have lower mean birth weights and higher rates of LBW, IUGR, and infant mortality (55–58). As discussed earlier, the effect of ETS on birth weight may not be uniform across the birth weight continuum. Even if the effect is uniform, the lower mean birth weight for poor women implies that additional adverse exposures might push birth weight into the more dangerous LBW range. In the workplace, poor women are more likely to hold jobs in which exposure levels are higher (such as in the service industry or in factories) and to be in workplaces in which they have little power to ask for environmental modifications. Poor women are more likely than other women to be undocumented workers, and whether or not legal residents, poor women are more likely to work in unregulated work environments such as garment sweatshops. With the enactment of the Personal Responsibility and Work Opportunity Reconciliation Act of 1996 (59) (also referred to as TANF, Temporary Assistance to Needy Families), more pregnant women from these disadvantaged groups will be in the workplace with little or no control over their working conditions except for government regulations (60). For all these reasons, ETS exposure is an issue of particular concern with regard to pregnancy outcomes in this population. Poor women are also more likely to be smokers themselves (61) and may be more likely to be exposed to other substances or conditions that increase the risk of LBW.

Conclusion

In summary, ETS exposure appears to have adverse effects on fetal growth parallel to what is seen for maternal smoking, but, as would be expected with less exposure, effects are generally smaller than those for maternal smoking. As a consequence, morbidity and mortality would be expected to be higher for infants born to women exposed to ETS during pregnancy. The workplace is one source of exposure to ETS for pregnant women that can and should be minimized to reduce risk of adverse pregnancy outcomes for working women.

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